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The Role of *Mycoplasma pneumoniae* in the pathogenesis of autoimmune diseases: Mechanisms, complications, and therapeutic perspectives

Anna Gwóźdź-Broczkowska*, **Paweł Godlewski**, **Aisha Hassan**, **Bartosz Górecki**

ABSTRACT

Mycoplasma pneumoniae is a respiratory pathogen capable of causing severe extrapulmonary complications, including the development of autoimmune diseases such as Guillain-Barré syndrome, systemic lupus erythematosus, and juvenile dermatomyositis. The pathogenic mechanisms involve molecular mimicry, activation of Toll-like receptors (TLRs) such as TLR2 and TLR4, and disruptions in cytokine regulation, including the overproduction of interleukin-17 (IL-17). Oxidative stress, inflammasome activation, and metabolic alterations in neutrophils further exacerbate inflammatory and autoimmune responses. Although the infection is usually not very severe, there is growing evidence that Mycoplasma pneumonia may be linked to the onset of autoimmune disorders. This emphasizesthe necessity for more studies on this infection. High levels of macrolide resistance, especially in Asia, and difficulties with diagnosis emphasize the need for new approaches to prevention and treatment. Studies have reported promising results with Qingfei Tongluo Formula (QTF). This traditional Chinese medicine reduces inflammation and mitigates the risk of autoimmunization by modulating oxidative stress and the PERK pathway. Future studies should consider Epstein-Barr virus (EBV) co-infection, which may synergistically increase the risk of autoimmune disease. The development of vaccines against *M. pneumoniae* is an important long-term avenue.

Keywords: *Mycoplasma pneumoniae*, autoimmunity, autoimmune diseases, Guillain-Barré syndrome, systemic lupus erythematosus, juvenile dermatomyositis, autoimmune complications of *Mycoplasma pneumoniae*

1. INTRODUCTION

Autoimmunity is currently a major challenge for medicine. Autoimmune diseases belong to a group of diverse diseases characterized by dysfunction of the immune system. The etiology is unknown, but it is suggested that in addition to genetic factors, environmental, hormonal, and immunological factors influence the development of autoimmune diseases. Among potential environmental triggers, bacterial and viral infections have been a focus of attention for years due to their ability to induce autoimmune processes, particularly in genetically predisposed individuals. Autoimmune diseases significantly impact individuals and their families while imposing substantial societal and healthcare costs. It is predicted that they will soon become one of the most common chronic disease (Miller, 2023).

In genetically susceptible individuals, environmental and hormonal factors such as UV radiation, infections, alcohol consumption, smoking, vitamin D deficiency, and exposure to chemicals can provoke the onset of autoimmune diseases (Mak and Tay, 2014). Scientists have identified more than 80 different autoimmune diseases. Interactions between genetics, age, gender, hormones, and environmental factors influence their development. (Selgrade et al., 1999). The likelihood of developing an autoimmune disease may depend on the child's age when the infection occurs. Recent studies suggest that early school-age children may be more likely to develop autoimmune diseases than younger children. Recent data suggest that the more mature the immune system, the more strongly it may respond to foreign pathogens, which increases the possibility of immune dysfunction (Ha et al., 2023).

The Role of Infectious Agents in Autoimmunity

Autoimmunity is when the host immune system attacks the body's structures, including cells and tissues, leading to chronic inflammation and organ damage (Smith and Germolec, 1999). Infectious agents, including bacteria, viruses, and parasites, are considered key triggers of autoimmune processes in genetically predisposed individuals. Mechanisms through which pathogens induce autoimmunity include molecular mimicry, epitope spreading, bystander activation, and alterations in antigen presentation. Examples of infections with autoimmune underpinnings include:

Coxsackie B virus: Autoimmune myocarditis,

Streptococcus pyogenes: Rheumatic fever,

Borrelia burgdorferi: Chronic arthritis in Lyme disease,

Herpes simplex virus: Stromal keratopathy,

Campylobacter jejuni: Guillain-Barré syndrome,

Trypanosoma cruzi: Chagasic cardiomyopathy (Ercolini and Miller, 2009).

In recent years, researchers have increasingly focused on the potential role of *Mycoplasma pneumoniae* in autoimmunity. This bacterium, commonly found worldwide, is primarily transmitted through human-to-human contact via aerosol droplets. It predominantly targets the mucosal membranes of the respiratory and urogenital tracts. Upon infection, *M. pneumoniae* attaches to ciliated epithelial cells, leading to localized tissue damage and the induction of immune responses (Kumar et al., 2019; Waites et al., 2017).

Characteristics of *Mycoplasma pneumoniae*

Mycoplasma pneumoniae is a Gram-negative bacterium belonging to the class *Mollicutes*. It lacks a cell wall, a feature that provides flexibility and renders it resistant to cell wall-targeting antibiotics, such as beta-lactams (Waites et al., 2005). Its genome is among the smallest prokaryotes, significantly limiting their metabolic capabilities and necessitating a parasitic lifestyle (Krause et al., 1982). In the absence of a cell wall, treatment relies on antibiotics such as macrolides, tetracyclines, and fluoroquinolones. In pediatric patients, clinicians prefer macrolides like azithromycin and clarithromycin due to their better tolerance and lower toxicity profiles (Lanao et al., 2023). *M. pneumoniae* is responsible for approximately 10% of all community-acquired pneumonia cases, including severe interstitial pneumonia (Khoury et al., 2016).

Although infections are typically mild, especially in children and adolescents, *M. pneumoniae* can cause various extrapulmonary complications involving the nervous, cardiovascular, dermatological, and hematological systems (Atkinson and Waites, 2014). Emerging evidence highlights the role of autoimmune phenomena in these complications. Numerous reports have documented

associations between *M. pneumoniae* infections and diseases such as Guillain-Barré syndrome, systemic lupus erythematosus, and certain forms of central nervous system inflammation. While the prognosis for respiratory-limited infections is generally favorable, rare cases can present with fulminant, multi-organ involvement, occurring in 0.2–0.5% of cases (Bajantri et al., 2018). Additionally, reinfection is possible shortly after the completion of treatment (Lanao et al., 2023).

2. METHODOLOGY

This study utilized medical databases, including PubMed, with the following English-language keywords: "*Mycoplasma pneumoniae*", "autoimmunity", "autoimmune diseases", "Guillain-Barré syndrome", "systemic lupus erythematosus", "juvenile dermatomyositis", and "autoimmune complications of *Mycoplasma pneumoniae*". The review focused on publications from 2012–2024, selected through the analysis of titles and abstracts focusing on the mechanisms of pathogenesis, links between *M. pneumoniae* and autoimmune diseases, and diagnostic and therapeutic approaches. Included were clinical studies, systematic reviews, and meta-analyses addressing autoimmune mechanisms induced by *M. pneumoniae*. Studies not directly addressing autoimmune mechanisms or autoimmune diseases associated with *M. pneumoniae* infection, as well as articles published in languages other than English, were excluded.

3. RESULTS & DISCUSSION

The Significance of *Mycoplasma pneumoniae* in the Context of Extrapulmonary Complications

Extrapulmonary complications occur in approximately 25% of patients infected with *Mycoplasma pneumoniae* and encompass a wide range of manifestations, including hepatitis, acute glomerulonephritis, and neurological disorders, making *M. pneumoniae* a particularly significant pathogen in medical practice (Curtiss et al., 2018). Researchers have observed that hemolytic anemia is a notable complication of *M. pneumoniae* infection, occurring more frequently in children than adults. Researchers believe that cross-reactive cold agglutinins mediate this effect. Additionally, there are reports of thrombotic thrombocytopenic purpura and disseminated intravascular coagulation. These may affect up to 50% of patients (Lanao et al., 2023).

About 14% of patients with *M. pneumoniae* infection involving synovial fluid have been documented to develop septic arthritis, arthralgia, osteoarthritis, or polyarthritis (Dash et al., 2018). Additionally, scientists have shown that *M. pneumoniae* affects the metabolism of high-density lipoproteins (HDL) by reducing their levels, which may be associated with the development of atherosclerosis and cardiovascular diseases. HDL has antioxidant, anti-inflammatory, and antithrombotic effects, thereby protecting the cardiovascular system. Infection with *M. pneumoniae* can increase the risk of cardiovascular events through inflammatory responses and oxidative stress, destabilizing atherosclerotic plaques and promoting thrombosis (Shen et al., 2024a).

Complications from *M. pneumoniae* infection can affect multiple organ systems, underlining the importance of considering this pathogen in a broad range of clinical contexts (Curtiss et al., 2018; Lanao et al., 2023). In Table 1, the extrapulmonary complications associated with *Mycoplasma pneumoniae* infection are listed. The mechanisms underlying the dissemination of *Mycoplasma pneumoniae* to extrapulmonary tissues are not fully understood. However, researchers hypothesize that direct tissue invasion and autoimmune processes have critical roles in this phenomenon (Curtiss et al., 2018).

Table 1 Extrapulmonary Complications Associated with *Mycoplasma pneumoniae* Infection

System	Complications
Gastrointestinal	Nausea, vomiting, hepatitis, pancreatitis
Urinary	Acute glomerulonephritis, renal failure
Auditory and Visual	External and middle ear infections, uveitis, optic disc edema, conjunctivitis, retinitis
Nervous	Guillain-Barré syndrome, central nervous system inflammations
Cardiovascular	Myocarditis, pericarditis

Pathomechanisms of *Mycoplasma pneumoniae* Infection

Pathogenic mechanisms associated with *M. pneumoniae* infection leading to autoimmunity include, among others, molecular and cellular processes (Ha et al., 2023). These mechanisms include, for example, modification of self-antigens, disruption of homeostasis, activation of specific signaling pathways, as well as oxidative stress. It is believed that molecular mimicry may play an important role in the initial autoimmune processes triggered by infection. The process of molecular mimicry is characterized by the structural or functional similarity of pathogen antigens to host autoantigens. This similarity can induce cross-reactivity, leading to the production of autoantibodies and the activation of T cells that attack host cells (Suliman, 2024). In *M. pneumoniae*, molecular mimicry plays a central role in initiating autoimmune responses.

The pathogen employs virulence factors such as adhesins, toxins, and metabolites to colonize and damage host tissues. Key adhesins, including P1, P30, P40/P90, and P116, facilitate attachment to sialic acid-containing receptors on respiratory epithelial cells, triggering inflammation and immune dysregulation (Nakane et al., 2015; Hu et al., 2022). These adhesins exhibit significant similarity to host autoantigens, leading to cross-reactive immune responses and autoimmunity (Ha et al., 2023). This phenomenon contributes to the pathogenesis of autoimmune diseases, including juvenile idiopathic arthritis as well as systemic lupus erythematosus by activating autoantibodies and cross-reactive lymphocytes (Ha et al., 2023). The virulence factors and metabolites of *M. pneumoniae* contribute to tissue damage through several mechanisms:

Oxidative Stress: Excess reactive oxygen species (ROS) generated during the inflammatory response causes cellular damage.

Cytotoxicity: The CARDS (Community-Acquired Respiratory Distress Syndrome) toxin and metabolites like hydrogen peroxide induce apoptosis and necrosis in host cells (Jiang et al., 2021). The CARDS toxin stimulates the production of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, leading to epithelial damage and increased vascular permeability (Wang et al., 2022).

NLRP3 Inflammasomes: These are activated by the CARDS toxin and ROS, resulting in the release of IL-1β and IL-18, which amplify inflammation and tissue damage (Hu et al., 2022).

Mycoplasma pneumoniae infection induces oxidative stress, which contributes to the formation of modified autoantigens (Georgakopoulou et al., 2024a). This process involves excessive production of reactive oxygen species (ROS) along with reactive nitrogen species (RNS), which leads to oxidative stress. The absence of ROS-neutralizing enzymes in *M. pneumoniae* results in the release of toxic metabolites, such as hydrogen peroxide (H_2O_2), which leads to damage of the respiratory epithelium, tissue breakdown, and impaired cilia function (Hu et al., 2022). Furthermore, impaired clearance of apoptotic cells increases exposure of the immune system to self-antigens and perpetuates inflammation (Georgakopoulou et al., 2024a).

In neutrophils, the Irg1/itaconate metabolic pathway suppresses the production of mitochondrial ROS, which helps to inhibit apoptosis and prolong the inflammatory response. Elevated levels of itaconate in bronchoalveolar lavage fluid (BALF) correlate with the severity of *M. pneumoniae* infection and susceptibility to possible autoimmune complications (Wang et al., 2024). This metabolic pathway influences the inflammatory process and the possibility of autoimmunity. Long non-coding RNAs (LncRNAs) play a key role in regulating the immune response during *M. pneumoniae* infections. These molecules can simultaneously support inflammatory reactions, protect the host from damage, and be exploited by the bacteria to evade the immune response.

LncRNA dysregulation during *M. pneumoniae* infection may contribute to the development of autoimmunity by enhancing the inflammatory response, activating the NF-κB signaling pathway, and epigenetic modifications of genes responsible for the regulation of immune tolerance (Yang et al., 2024). Non-coding RNA may play an important role in pathogen survival and host immune dysregulation. In Table 2, the key lncRNAs involved in regulating inflammatory responses are presented.

Table 2 Examples of lncRNAs Involved in Regulating Inflammatory Responses

Name of lncRNA	Function
GAS5	Reduces inflammatory response and protects against tissue damage.
HAGLROS	Regulates NF-κB pathway, which is important in inflammation.
MALAT1	Promotes NF-κB activation and reduces inflammation by inhibiting it.

Toll-like receptors (TLRs) play an important role in immune dysregulation during *Mycoplasma pneumoniae* infection. Bacterial lipoproteins activate Toll-like receptors (TLR1, TLR2, TLR6) that recognize pathogen-associated molecular patterns (PAMPs), stimulating the release of pro-inflammatory cytokines (Zhu et al., 2023). TLR2 supports bacterial elimination by activating pro-inflammatory cytokines such as TNF-α and IL-8. However, excessive activation of TLR2 can lead to complications such as bronchial hyperreactivity, overproduction of mucus in the airways, and tissue damage caused by reactive oxygen species (ROS). Overactivation of TLR2 is one of the key factors leading to the onset of inflammatory complications.

Similarly, TLR4 recognizes *M. pneumoniae* and researchers have associated its overexpression with severe conditions such as acute myocardial infarction. Although it is not well understood, the role of other TLR receptors (e.g., TLR3, TLR7, TLR8, TLR9) in the context of *M. pneumoniae* is suggested to be involved in immune responses (Naghib et al., 2018). Interleukin 17 (IL-17) is produced mainly by Th17 lymphocytes and plays an important role in the body's immune system and ability to defend against *Mycoplasma pneumoniae*. IL-17 activates neutrophils and stimulates the production of antimicrobial peptides that help eliminate the pathogen.

However, an excess of IL-17 can lead to chronic inflammation, tissue damage, and exacerbation of chronic diseases such as asthma and bronchiolitis. An imbalance between Th17 lymphocytes and Treg cells, with a predominance of Th17 cells, is commonly observed in severe cases of pneumonia caused by *M. pneumoniae*. High levels of IL-17 are a marker for the severity of infection and the risk of complications. Targeted therapies against IL-17 may be effective, but they require caution to avoid impairing the immune response to other infections (Luo et al., 2021). Inflammasomes, particularly NLRP3, are critical in enhancing the inflammatory response during *M. pneumoniae* infection.

Inflammasomes are activated by community-acquired respiratory syndrome (CARDS) toxins and reactive oxygen species (ROS) produced by bacteria. Inflammasome activation causes caspase-1 to activate, mature, and excrete proinflammatory cytokines, including IL-1β and IL-18. This process may result in pyroptosis, a programmed cell death, which further exacerbates tissue destruction and inflammation. CARDS toxin, a potent virulence factor, increases vascular permeability, damages the respiratory epithelium, and stimulates the production of cytokines such as TNF-α. CARDS expression correlates with severe forms of pneumonia, such as refractory pneumonia (RMPP), and may serve as a diagnostic marker of infection severity (Hu et al., 2022).

In mild cases of infection, increased neutrophil activity supports immune defense. However, in severe cases, "exhausted" CD8+ T lymphocytes and dysfunction of CD4+ T lymphocytes occur due to chronic interferon type I signaling. Additionally, M1 and M2 macrophages are activated, triggering pro-inflammatory responses and immunosuppression. Possible therapeutic avenues include S100A8/A9 molecules and PD-1/PD-L1 immune checkpoint pathway inhibitors, which may improve T cell function (Shen et al., 2024b). Studies have shown that the presence of *M. pneumoniae*-specific CD4+ effector memory cells (TEM) correlates with the severity of lung inflammation. Excessive Th1 activation, even after symptom resolution, can lead to persistent inflammation and tissue damage.

These mechanisms resemble those seen in autoimmune diseases, suggesting that *M. pneumoniae* may initiate such conditions (Pánisová et al., 2021). Neutrophils constitute a crucial element in the response to *Mycoplasma pneumoniae* (MP) through phagocytosis, degranulation, and the formation of NETs (Neutrophil Extracellular Traps), which help eliminate pathogens but may also cause tissue damage when excessively activated. The IL-23/IL-17 axis and granulocyte-colony stimulating factor (G-CSF) drive the recruitment of neutrophils to the lungs, while the CARDS toxin intensifies the inflammatory response and promotes neutrophil infiltration. Excessive production of ROS and NETs leads to oxidative stress and lung damage.

Age and immune deficiencies influence the ability of neutrophils to mount an effective immune response, increasing the risk of severe disease and extrapulmonary manifestations of MP, such as arthritis, neurological disorders, or cardiovascular diseases. These complications are partly due to autoimmune mechanisms and the formation of immune complexes (Fan et al., 2024). *M. pneumoniae* also affects neutrophil metabolism by activating the Irg1/itaconate pathway, which reduces the production of mitochondrial ROS (mtROS). The reduction in mtROS limits the bactericidal activity of neutrophils and hinders their apoptosis, prolonging the inflammatory state and facilitating the modification of autoantigens (Wang et al., 2024).

Genomic studies of *M. pneumoniae* have shown that macrolide resistance is primarily associated with mutations in the 23S rRNA region (2063 A→G and 2064 A→G). Erythromycin-resistant strains lead to more severe pneumonia, requiring intensive treatment. Two genetic types of strains are distinguished: P1-type I and P1-type II. Mutations in the L4 and CARDS genes are found exclusively in P1-type II strains, making them more pathogenic (Jiang et al., 2024). Additionally, *M. pneumoniae* induces the formation of immune complexes that can deposit in tissues (e.g., kidneys, joints, blood vessels), triggering local inflammatory reactions characteristic of systemic lupus erythematosus or IgA vasculitis (Ha et al., 2023).

Clinical Evidence Linking *Mycoplasma pneumoniae* and Autoimmune Diseases

Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuropathy belonging to autoimmune diseases in which the immune system attacks the myelin sheath of peripheral nerves. It manifests itself with rapidly progressive muscle weakness and dysreflexia (Willison et al., 2016). Studies indicate that *M. pneumoniae* accounts for 3–14% of GBS cases, particularly in children and young adults (Meyer-Sauteur et al., 2018). A key pathogenic mechanism is molecular mimicry of bacterial galactolipids (e.g., galactosyl diacylglycerol - GalGalDAG) with human glycosphingolipids, such as galactocerebroside (GalCer), present in nerve myelin (Broto et al., 2024). The glycolipid antigens of *M. pneumoniae* may mimic gangliosides on nerve cells, leading to the production of autoantibodies and demyelination.

This phenomenon underlies the autoimmune response in GBS, where antibodies against GalCer and other bacterial lipids cross-react with nerve tissues. Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that is characterized by the involvement of multiple organs, including the kidneys and heart, skin, and even joints. Women between the ages of 20 and 40 are most often affected, and the symptoms include fatigue, joint pain, skin rashes, and dysfunction of internal organs (Aringer and Petri, 2020). Evidence suggests that *M. pneumoniae* infection increases the risk of developing SLE, which results from molecular mimicry, induction of pro-inflammatory cytokines (e.g., IL-1, IL-6, IFN-α), and activation of autoreactive T and B lymphocytes (Chu et al., 2022).

Studies have also shown that patients with newly diagnosed SLE were more likely to have had *M. pneumoniae* infections, indicating a role for the pathogen initiating and exacerbating disease symptoms, such as lupus nephritis (Bajantri et al., 2017). Juvenile Dermatomyositis (JDM) is a rare disease that affects the muscles and skin. It is termed "juvenile" when it begins before the age of 16. Researchers refer to it as 'juvenile' when it starts before the age of 16. The disease affects the small blood vessels within the skin and muscles. Muscle weakness or pain, especially in the trunk, hips, shoulders, and neck, characterizes it. Most patients also present with a characteristic rash, which may occur in multiple body areas: on the face, eyelids, joints of the hands, knees, and elbows (McCann et al., 2022).

Researchers have noted that *M. pneumoniae* infections can trigger juvenile dermatomyositis (JDM) by activating the immune system and damaging blood vessels. Clinical case reports have shown a connection between infection and symptoms such as muscle weakness, pain, and skin changes (Sassetti et al., 2024). These mechanisms include macrophage activation, cytokine production and the development of immune complexes, potentially resulting in muscle and blood vessel damage. Children with pneumonia caused by *M. pneumoniae* and fever are more likely to have a concurrent Epstein-Barr virus (EBV) infection, a well-known trigger for autoimmune responses. EBV can enhance the inflammatory response by activating B cells and producing cytokines.

Dual infection, i.e., EBV infection concurrently with *M. pneumoniae*, can potentiate autoimmune responses (Li et al., 2024). Modern techniques, including genomic sequencing and proteomic analysis, permit for the identity of unique M. Pneumoniae antigens liable for inducing autoimmunization. The results of those research may lead to the development of recent diagnostic markers and targeted healing procedures (Jiang et al., 2024). Understanding the function of the CARDS toxin and the mechanisms of neutrophil recruitment may additionally allow the development of focused treatment plans, which include neutralizing IL-23/IL-17 or blockading the CARDS toxin, which can lessen excessive inflammatory responses and tissue harm (Fan et al., 2024).

Qingfei Tongluo Formula (QTF) is a conventional Chinese method that reduces infection, oxidative strain (ROS), and endoplasmic reticulum (ER) strain through inhibiting the PERK pathway. The movement of QTF decreases the manufacturing of seasoned-inflammatory cytokines, consisting of TNF-α and IL-eight, limits tissue harm, and decreases the chance of apoptosis, thereby supporting immune homeostasis. Research carried out using cell and animal fashions has revealed the effectiveness of QTF in alleviating symptoms of pneumonia because of *M. pneumoniae* and in decreasing the hazard of autoimmunization (Liu et al., 2022).

In China, the predominant *M. pneumoniae* strains are ST3 (69.79%) and ST14 (19.46%), with a high level of macrolide resistance (88.1%) due to the A2063G mutation in the 23S rRNA gene. Researchers have found that macrolide-sensitive ST7 strains are usually located in the southern regions of the country. Following the lifting of pandemic restrictions, researchers have reported local outbreaks and whole-genome sequencing has become a key tool in epidemiological monitoring and identifying resistant strains (Chen et al., 2024).

Therapeutic Challenges and Future Therapies

The treatment of *M. pneumoniae* infections relies on using antibiotics that penetrate cells, such as macrolides (e.g., azithromycin). Alternatives include tetracyclines and fluoroquinolones; however, using them in younger patients may lead to side effects such as tooth

discoloration or tendinopathy. The growing macrolide resistance, particularly in Asia, has led to prolonged treatment durations and the necessity of using alternative antibiotics (Georgakopoulou et al., 2024b). It is important to develop vaccines against *M. pneumoniae* in order to prevent possible infections with the pathogen and reduce the risk of developing autoimmune diseases (Vizarraga et al., 2020; Kant et al., 2024). Introducing rapid and sensitive diagnostic methods, such as PCR and artificial intelligence, will enable early detection of infections and the initiation of appropriate treatment (Kant et al., 2024).

4. CONCLUSION

Mycoplasma pneumoniae represents a major pathogen contributing to severe extrapulmonary complications, including autoimmune diseases such as Guillain-Barré syndrome, systemic lupus erythematosus (SLE), and juvenile dermatomyositis (JDM). The pathogenic mechanisms involve molecular mimicry, dysregulation of cytokines such as IL-17, and oxidative stress, which promotes the formation of modified autoantigens. Chronic infection leads to the loss of immunological tolerance and can trigger autoimmune responses. High macrolide resistance and the absence of vaccines require developing new therapeutic strategies.

Immunomodulation, early molecular diagnostics, and vaccine development are crucial elements in reducing the risk of complications. Studies on Qingfei Tongluo Formula (QTF) have shown its potential in reducing inflammation and limiting the risk of autoimmunization. Future studies on autoimmunity caused by *M. pneumoniae* should also take into account co-infection with Epstein-Barr virus, because both of these pathogens are responsible for the development of autoimmune diseases, and their co-occurrence may enhance the body's immune response. Additional studies are indispensable to fully elucidate the precise mechanisms that explain why some patients develop these complications while others do not.

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Not applicable.

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Not applicable.

Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

REFERENCES

1. Aringer M, Petri M. New classification criteria for systemic lupus erythematosus. Curr Opin Rheumatol 2020; 32(6):590-596. doi: 10.1097/BOR.0000000000000740

2. Atkinson TP, Waites KB. *Mycoplasma pneumoniae* Infections in Childhood. Pediatr Infect Dis J 2014; 33(1):92-4. doi: 10.1097/INF.0000000000000171

3. Bajantri B, Danial S, Duncalf R, Khaja M. Rare complicated parapneumonic effusion, *Mycoplasma pneumoniae* with new-onset lupus flare: Case report and literature review. Respir Med Case Rep 2017; 22:287-291. doi: 10.1016/j.rmcr.2017.10.010

4. Bajantri B, Venkatram S, Diaz-Fuentes G. *Mycoplasma pneumoniae*: A Potentially Severe Infection. J Clin Med Res 2018; 10(7):535-544. doi: 10.14740/jocmr3421w

5. Broto A, Piñero-Lambea C, Segura-Morales C, Tio-Gillen AP, Unger WWJ, Burgos R, Mazzolini R, Miravet-Verde S, Jacobs BC, Casas J, Huizinga R, Lluch-Senar M, Serrano L. Engineering *Mycoplasma pneumoniae* to bypass the association with Guillain-Barré syndrome. Microbes Infect 2024; 26(5-6):105342. doi: 10.1016/j.micinf.2024.105342

6. Chen Y, Li X, Fu Y, Yu Y, Zhou H. Whole-genome sequencing unveils the outbreak of *Mycoplasma pneumoniae* in mainland China. Lancet Microbe 2024; 5(9):100870. doi: 10.1016/S2666-5247(24)00086-7

7. Chu KA, Ou TY, Hung WH, Sung J, Chen W, Lin CL, Hung YM, Wei JC. Mycoplasma pneumonia Infection Is Associated with an Increased Risk of Systemic Lupus Erythematosus: A Nationwide, Retrospective Cohort Study. Front Microbiol 2022; 13:815136. doi: 10.3389/fmicb.2022.815136

8. Curtiss P, Melnick L, Sicco KL, Liebman TN. *Mycoplasma pneumoniae*, more than a lung disease. Dermatol Online J 2018; 24(6):13030/qt8w993185.

9. Dash S, Chaudhry R, Dhawan B, Dey AB, Kabra SK, Das BK. Clinical spectrum and diagnostic yields of *Mycoplasma pneumoniae* as a causative agent of community-acquired pneumonia. J Lab Physicians 2018; 10(1):44-49. doi: 10.4103/JLP.JLP_62_17

10. Ercolini AM, Miller SD. The role of infections in autoimmune disease. Clin Exp Immunol 2009; 155(1):1-15. doi: 10.1111/j.1365-2249.2008.03834.x

11. Fan L, Xu N, Guo Y, Li L. Enhanced insights into the neutrophil-driven immune mechanisms during *Mycoplasma pneumoniae* infection. Heliyon 2024; 10(21):e38950. doi: 10.1016/j.heliyon.2024.e38950

12. Georgakopoulou VE, Lempesis IG, Sklapani P, Trakas N, Spandidos DA. Exploring the pathogenetic mechanisms of *Mycoplasma pneumoniae* (Review). Exp Ther Med 2024a; 28(1):271. doi: 10.3892/etm.2024.12559

13. Georgakopoulou VE, Lempesis IG, Tarantinos K, Sklapani P, Trakas N, Spandidos DA. Atypical pneumonia (Review). Exp Ther Med 2024b; 28(5):424. doi: 10.3892/etm.2024.12713

14. Ha EK, Kim JH, Cha HR, Han BE, Shin YH, Baek HS, Choi SH, Han MY. Investigating the occurrence of autoimmune diseases among children and adolescents hospitalized for *Mycoplasma pneumoniae* infections. Front Immunol 2023; 14: 1165586. doi: 10.3389/fimmu.2023.1165586

15. Hu J, Ye Y, Chen X, Xiong L, Xie W, Liu P. Insight into the Pathogenic Mechanism of *Mycoplasma pneumoniae*. Curr Microbiol 2022; 80(1):14. doi: 10.1007/s00284-022-03103-0

16. Jiang Y, Kang H, Dou H, Guo D, Yuan Q, Dong L, Du Z, Zhao W, Xin D. Comparative genomic sequencing to characterize *Mycoplasma pneumoniae* genome, typing, and drug resistance. Microbiol Spectr 2024; 12(8):e0361523. doi: 10.1128/spectrum.03615-23

17. Jiang Z, Li S, Zhu C, Zhou R, Leung PHM. *Mycoplasma pneumoniae* Infections: Pathogenesis and Vaccine Development. Pathogens 2021; 10(2):119. doi: 10.3390/pathogens10020119

18. Kant R, Kumar N, Malik YS, Everett D, Saluja D, Launey T, Kaushik R. Critical insights from recent outbreaks of *Mycoplasma pneumoniae*: decoding the challenges and effective interventions strategies. Int J Infect Dis 2024; 147:107 200. doi: 10.1016/j.ijid.2024.107200

19. Khoury T, Sviri S, Rmeileh AA, Nubani A, Abutbul A, Hoss S, van Heerden PV, Bayya AE, Hidalgo-Grass C, Moses AE, Nir-Paz R. Increased rates of intensive care unit admission in patients with *Mycoplasma pneumoniae*: a retrospective study. Clin Microbiol Infect 2016; 22(8):711-4. doi: 10.1016/j.cmi.2016.05.028

20. Krause DC, Leith DK, Wilson RM, Baseman JB. Identification of *Mycoplasma pneumoniae* proteins associated with hemadsorption and virulence. Infect Immun 1982; 35(3):809-17. doi: 10.1128/iai.35.3.809-817.1982

21. Kumar S, Roy RD, Sethi GR, Saigal SR. *Mycoplasma pneumoniae* infection and asthma in children. Trop Doct 2019; 49(2):117-119. doi: 10.1177/0049475518816591

22. Lanao AE, Chakraborty RK, Pearson-Shaver AL. Mycoplasma Infections. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.

23. Li J, Zhang H, Guo J, Ma X. Clinical features of *Mycoplasma pneumoniae* pneumonia in children without fever. BMC Pediatr 2024; 24(1):52. doi: 10.1186/s12887-023-04512-1

24. Liu X, Wang M, Kan Q, Lin Y, Jiang Z. Qingfei Tongluo Formula Mitigates *Mycoplasma pneumoniae* Infection via the PERK Signaling Pathway. Dis Markers 2022; 2022:9340353. doi: 10.1155/2022/9340353

25. Luo Y, Li C, Zhou Z, Gong Z, Zhu C, Lei A. Biological functions of IL-17-producing cells in mycoplasma respiratory infection. Immunology 2021; 164(2):223-230. doi: 10.1111/imm.13346

26. Mak A, Tay SH. Environmental factors, toxicants and systemic lupus erythematosus. Int J Mol Sci 2014; 15(9):16043-56. doi: 10.3390/ijms150916043

27. McCann LJ, Livermore P, Wilkinson MGL, Wedderburn LR. Juvenile dermatomyositis. Where are we now? Clin Exp Rheumatol 2022; 40(2):394-403. doi: 10.55563/clinexprheumatol/56ilob

28. Meyer-Sauteur PM, Huizinga R, Tio-Gillen AP, Drenthen J, Unger WWJ, Jacobs E, Van-Rossum AMC, Jacobs BC. Intrathecal antibody responses to GalC in Guillain-Barré syndrome triggered by *Mycoplasma pneumoniae*. J Neuroimmunol 2018; 314:13–16. doi: 10.1016/j.jneuroim.2017.11.011

29. Miller FW. The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention. Curr Opin Immunol 2023; 80:102266. doi: 10.1016/j.coi.2022.102266

30. Naghib M, Hatam-Jahromi M, Niktab M, Ahmadi R, Kariminik A. *Mycoplasma pneumoniae* and toll-like receptors: A mutual avenue. Allergol Immunopathol (Madr) 2018; 46(5):508-513. doi: 10.1016/j.aller.2017.09.021

31. Nakane D, Kenri T, Matsuo L, Miyata M. Systematic Structural Analyses of Attachment Organelle in *Mycoplasma pneumoniae*. PLoS Pathog 2015; 11(12):e1005299. doi: 10.1371/journal.ppat.1005299

32. Pánisová E, Unger WWJ, Berger C, Meyer Sauteur PM. *Mycoplasma pneumoniae* -Specific IFN-γ-Producing CD4+ Effector-Memory T Cells Correlate with Pulmonary Disease. Am J Respir Cell Mol Biol 2021; 64(1):143-146. doi: 10.1165/rcmb.2020-0237LE

33. Sassetti C, Borrelli C, Mazuy M, Turrini I, Rigante D, Esposito S. The relationship between infectious agents and juvenile dermatomyositis: a narrative update from the pediatric perspective. Front Immunol 2024; 15:1377952. doi: 10.3389/fimmu.2024.1377952

34. Selgrade MK, Cooper GS, Germolec DR, Heindel JJ. Linking environmental agents and autoimmune disease: an agenda for future research. Environ Health Perspect 1999; 107 Suppl 5(Suppl 5):811-3. doi: 10.1289/ehp.99107s5811

35. Shen T, Li Y, Liu T, Lian Y, Kong L. Association between *Mycoplasma pneumoniae* infection, high-density lipoprotein metabolism and cardiovascular health (Review). Biomed Rep 2024a; 20(3):39. doi: 10.3892/br.2024.1729

36. Shen X, Jin Z, Chen X, Wang Z, Yi L, Ou Y, Gong L, Zhu C, Xu G, Wang Y. Single-cell transcriptome atlas revealed bronchoalveolar immune features related to disease severity in pediatric *Mycoplasma pneumoniae* pneumonia. MedComm 2024b; 5(10):e748. doi: 10.1002/mco2.748

37. Smith DA, Germolec DR. Introduction to immunology and autoimmunity. Environ Health Perspect 1999; 107 Suppl 5(Suppl 5):661-5. doi: 10.1289/ehp.99107s5661

38. Suliman BA. Potential clinical implications of molecular mimicry-induced autoimmunity. Immun Inflamm Dis 2024; 12(2):e1178. doi: 10.1002/iid3.1178

39. Vizarraga D, Kawamoto A, Matsumoto U, Illanes R, Pérez-Luque R, Martín J, Mazzolini R, Bierge P, Pich OQ, Espasa M, Sanfeliu I, Esperalba J, Fernández-Huerta M, Scheffer MP, Pinyol J, Frangakis AS, Lluch-Senar M, Mori S, Shibayama K, Kenri T, Kato T, Namba K, Fita I, Miyata M, Aparicio D. Immunodominant proteins P1 and P40/P90 from human pathogen *Mycoplasma pneumoniae*. Nat Commun 2020; 11(1):5188. doi: 10.1038/s41467-020-18777-y

40. Waites KB, Katz B, Schelonka RL. Mycoplasmas and ureaplasmas as neonatal pathogens. Clin Microbiol Rev 2005; 18(4):757-89. doi: 10.1128/CMR.18.4.757-789.2005

41. Waites KB, Xiao L, Liu Y, Balish MF, Atkinson TP. *Mycoplasma pneumoniae* from the Respiratory Tract and Beyond. Clin Microbiol Rev 2017; 30(3):747-809. doi: 10.1128/ CMR.00114-16

42. Wang C, Wen J, Yan Z, Zhou Y, Gong Z, Luo Y, Li Z, Zheng K, Zhang H, Ding N, Wang C, Zhu C, Wu Y, Lei A. Suppressing neutrophil itaconate production attenuates *Mycoplasma pneumoniae* pneumonia. PLoS Pathog 2024; 20(11):e1012614. doi: 10.1371/journal.ppat.1012614

43. Wang T, Sun H, Lu Z, Jiang W, Dai G, Huang L, Wang M, Zhu C, Wang Y, Hao C, Yan Y, Chen Z. The CARDS toxin of *Mycoplasma pneumoniae* induces a positive feedback loop of type 1 immune response. Front Immunol 2022; 13:1054788. doi: 10.3389/fimmu.2022.1054788

44. Willison HJ, Jacobs BC, Van-Doorn PA. Guillain-Barré syndrome. Lancet 2016; 388(10045):717-27. doi: 10.1016/S0140-6736(16)00339-1

45. Yang Z, Zhou J, Su N, Zhang Z, Chen J, Liu P, Ling P. Insights into the defensive roles of lncRNAs during *Mycoplasma pneumoniae* infection. Front Microbiol 2024; 15:1330660. doi: 10.3389/fmicb.2024.1330660

46. Zhu Y, Luo Y, Li L, Jiang X, Du Y, Wang J, Li H, Gu H, Li D, Tang H, Qin H, Xu C, Liu Y, Zhao D, Guo Y, Liu F. Immune response plays a role in *Mycoplasma pneumoniae* pneumonia. Front Immunol 2023; 14:1189647. doi: 10.3389/fimmu.2023.1189647